UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/360,199	07/23/99	GAULDIE J	GDI-1

HM22/0131

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EXAMINER	
SCHNIZER,R	
ART UNIT	**PAPER NUMBER**
1632	7

DATE MAILED: 01/31/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/360,199	GAULDIE ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

An amendment was received and entered as Paper No.6 on 11/13/00. Applicant's election with traverse of the species of a protein in claim 2; to a tumor antigen in claim 5 an antigen encoded by a pathogen in claim 19 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-28 remain pending in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19, 26, 27, and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for delivery of a nucleic acid encoding PymT antigen to gastrointestinal or genitourinary cells comprising the step of disrupting the mucosa covering the target cells, wherein the method results in proliferation of cytotoxic T lymphocytes specific for Pym T antigen, does not reasonably provide enablement for any therapeutic or preventive utility such as gene therapy or genetic immunization. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Briefly, claims 1-19, are drawn to methods using a pharmaceutical composition, and claims 27 and 28 are drawn to methods for treating or preventing a pathological condition. The composition and methods comprise nucleic acids as the pharmaceutically active agent. Claim 26 is drawn to a suppository comprising a nucleic acid, wherein the suppository induces an immune response in an individual.

For the purpose of examination under 35 U.S.C. 112, first paragraph, a pharmaceutical composition is considered to be one which provides a therapeutic effect when delivered. Because the purpose of delivering such compositions is to perform therapy, each of claims 1-19, 27, and 28 reads on a method of nucleic acid-mediated therapy. The scope of the claims also encompasses the treatment of any disease in any organism with a gastrointestinal tract. Claim 26 is included in this rejection because the only purpose for inducing an immune response in vivo asserted by the specification is therapeutic in nature, *e.g.* gene therapy or genetic immunization.

The amended claims raise new enablement issues. Claims 1-19 now require enablement in all genitourinary cells. Steadman's Medical Dictionary defines "genitourinary" as "[r]elating to the organs of reproduction and urination. This definition comprises all cells in the genitals, including those not immediately associated with the urinary tract, *e.g.* sertoli cells, erectile tissue, and muscle cells. The claims now encompass the expression of antisense RNAs which must induce a therapeutic immune response, as well as proteins which must effect desired biological

functions while also producing a therapeutic immune response. According to claim 4, the desired biological function must be other than, and thus in addition to, the induction of an immune response.

The specification provides no *in vivo* example of the invention in which a protective immune response is demonstrated, and does not demonstrate transfection of any cells other than colon epithelial cells. As noted previously, and below, the immune response obtainable by genetic immunization is highly dependent on the route of immunization and the target cells which are transfected. The therapeutic effects of such immunizations are highly unpredictable, and enablement of such methods must be considered in the context of each antigen, each expression construct, and each mode of delivery. With respect to the breadth of antigens encompassed by the claims, the specification offers no examples of any antigenic antisense RNAs or any protein which provides a desirable biological function in addition to functioning as an antigen which provides a therapeutic immune response. In the absence of any working example or any guidance as to how to ensure a therapeutic response, and in view of the unpredictable state of the art, one of skill in the art would have to perform undue experimentation in order to produce a therapeutic immune response using any and all antigens encompassed by the instant invention.

Applicant argues that the specification provides adequate support for generation of a therapeutic immune response using the methods of the invention. Against the examiner's argument that no demonstration of any *in vivo* therapeutic immune response was demonstrated, Applicant argues that the results of an *in vitro* CTL assay are sufficient to indicate therapeutic

relevance because CTL assays are the currently accepted experimental technique for determining the efficacy of a given vaccine. Applicant argues that these *in vitro* results were discounted without any cogitative, scientific basis.

Applicant's position that CTL assays are the currently accepted experimental technique for determining the efficacy of a given vaccine is unsupported by any evidence of record. While CTL assays can be suggestive of potential therapeutic efficacy, they are not sufficient to allow one to accurately predict the therapeutic effect of the instant invention. In contrast, Wan (as discussed below) teaches an assay wherein mice are challenged with tumor cells after innoculation with a vaccine. This *in vivo* assay provides objective proof of the efficacy of Wan's method in the mouse. The results of the CTL assays in the specification have not been discounted by the examiner. Rather, a judgement was made that the results of these assays could not support a prediction that a therapeutic immune response could be achieved with the claimed methods *in vivo*. This judgement is supported by the state of the prior art, and the acknowledged unpredictability of the art. It has been established *in vitro* cytotoxic T lymphocyte (CTL) assays are not, in and of themselves, predictive of *in vivo* CTL killing. This is supported by the teachings of Bachmann et al. and Lancki et al. Bachmann et al. compare the CTL results based on *in vitro* restimulation and cells removed from virus infected animals and found drastic differences in 51CR-release CTL results. Bachmann cautions that *in vitro* CTL responses need to be confirmed by *in vivo* results to be considered biologically relevant (see entire article, specifically page 323 second column under Conclusion). Lancki et al. states, "It is not certain how the capacity of a

CTL effector to lyse a target cell *in vitro* as measured by the release of radiolabelled macromolecules relates to the capacity of CTL to kill such target cells *in vivo* (page 72, first column) and goes on to state that the properties of CTLs have been studied mostly in unidirectional *in vitro* mixed lymphocyte assays. To further highlight the unpredictability of the art, Wan teaches that the protective immune response was obtained *in vivo* by inoculating mice with adenovirus modified to express PymT antigen was highly dependent on the route of administration. Wan investigated several different routes, none of which is employed in the instant examples. Applicant, while acknowledging that the physiological art is highly unpredictable, has not provided sufficient evidence or reasoning to support the position that a protective immune response will be generated by the method of the instant invention. It is further noted that only one of Applicant's claims is limited to a method of raising an immune response against a PymT antigen, whereas the rest of the claims are substantially broader and encompass the treatment of any disease with any antigen. In view of the unpredictability of the art and the lack of any *in vivo* working example in any animal, the rejection is maintained as proper.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Henning et al (WO 93/19660, published 10/14/93).

Henning teaches a method for delivering biologically active genes to the intestinal epithelium wherein the genes are expressed. See entire document, especially abstract. The nucleic acids may be delivered with a mucolytic agent. See page 11, lines 25-28; and claims 61 and 62 on page 36. The nucleic acid may be comprised within a slow-release capsule. See claim 12, lines 4-8 of page 30. The method may be repeated. See claim 37, lines 1-7 of page 33.

Thus Henning anticipates the claims.

Applicant argues that the cited art fails to anticipate the claims as amended, because the Henning fails to teach the use of ethanol as a mucodisruptive agent. This is unpersuasive because Applicant failed to direct the entry of any amendment to claims 20-25, and they remain in their original form. In the event that such an amendment had been entered, an obviousness rejection would have been set forth over Henning in view of Wallace (Gastroenterology 91(3):603-611, 9/1986), the abstract of which is provided here as a courtesy to Applicant. Wallace teaches the use of 50% ethanol as a mucodisruptive agent. Because Henning teaches the use of a mucodisruptive agent in order to facilitate gene delivery to intestinal cells, it would have been obvious to substitute 50% ethanol for the agent of Henning.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached on Mondays and Thursdays between the hours of 6:20 AM and 3:50 PM, and on Tuesdays, Wednesdays and Fridays between the hours of 7:00 AM and 4:30 PM (Eastern time). The examiner is off every other Friday, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Questions regarding formal matters may be directed to the Patent Analyst, Patsy Zimmerman, whose telephone number is 703-305-2758.

Richard Schnizer, Ph. D.

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